Appendix A Supplementary Materials

Captions for Supplementary Materials

Table 1: Summary of Clinical Adverse Experiences from SPS and ZEST Trials in Subjects Who Received ZVL or Placebo (0-42 Days Postvaccination)

Table 2: Vaccine-Related Injection-Site Reactions Reported in SPS and ZEST Trials in ≥1% of Subjects Who Received ZVL or Placebo (0-42 Days Postvaccination)

Annex 1: Key Exclusion Criteria for SPS and ZEST and MSD Clinical Trial Safety Data: Two Reports of VZV Oka/Merck Vaccine-strain, Confirmed by PCR

Annex 2: Overview of Safety from Post-marketing Observational Studies

Annex 3: Post-marketing Surveillance for Reports from the Literature and MedDRA Preferred Terms Selected in the Review of Post-marketing Reports of Common and Selected Adverse Experiences

Table 3: Post-marketing Reports (N=45) of Fatal Outcome Containing Sufficient Medical Information and/or Cause of Death from Market Introduction (02-May-2006) through 01-May-2016

Table 4: Summary of 10 Reports of Ophthalmic Herpes Zoster (HZO) in Patients with a Prior History of HZO

Table 5a: Summary of Post-marketing Reports of Encephalitis Received From Market Introduction (2-May-2006) Through 1-May-2016

Table 5b: Summary of Post-marketing Reports of Acute Disseminated Encephalomyelitis (ADEM) Received From Market Introduction (2-May-2006) Through 1-May-2016

Figure 1: Post-marketing Reports of Fatal Outcome Temporally-associated with Vaccination with ZVL and Reported by Cause of Death

Supplementary Table 1:

Supplementary Table 1: Summary of Clinical Adverse Experiences from SPS and ZEST Trials in Subjects Who Received ZVL or Placebo (0-42 Days Postvaccination)

	SPS[a]		ZEST[a]	
Subjects in population with safety follow-up	**ZVL** (N = 3345) %	**Placebo** (N = 3271) %	**ZVL** (N =11,094) %	**Placebo** (N = 11,116) %
with one or more AEs	58.1	34.4	72.8	41.5
injection-site	48.3	16.6	63.9	14.4
systemic	24.7	23.6	35.4	33.5
serious	1.9	1.3	0.6	0.5
with vaccine-related[b] AEs	50.2	19.7	65.0	17.9
injection-site	48.2	16.5	63.9	14.4
systemic	6.3	4.9	6.7	4.7
serious[c]	0	0	0	0

[a] In SPS, subjects ≥60 years of age received a single dose of either ZVL (n=19,270) or placebo (n=19,276); data presented is from the Adverse Event Monitoring Substudy of SPS (n=3,345 received ZVL and n=3,271 received placebo). [3] In ZEST, subjects 50-59 years of age received a single dose of either ZVL (n=11,184) or placebo (n=11,212).[4] Subjects in the Adverse Event Monitoring Substudy of SPS and all subjects enrolled in ZEST were provided a vaccination report card to record AEs occurring through approximately 42 days postvaccination [3, 4, 11].

[b] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

[c] In SPS, a total of 4 vaccine-related serious AEs occurred within 42 days postvaccination [2 (0%) in the ZVL group (asthma exacerbation and polymyalgia rheumatic) and 2 (0%) in the placebo group (anaphylactic reaction and polymyalgia rheumatic)]. In ZEST, only 1 (0%) vaccine-related serious AE occurred within 42 days postvaccination (anaphylactic reaction reported by a ZVL recipient).

Supplementary Table 2:

Supplementary Table 2: Vaccine-Related Injection-Site Reactions Reported in SPS and ZEST Trials in ≥1% of Subjects Who Received ZVL or Placebo (0-42 Days Postvaccination)

	SPS		ZEST	
Injection-Site AEs	**ZVL** (N = 3345) %	**Placebo** (N = 3271) %	**ZVL** (N =11,094) %	**Placebo** (N = 11,116) %
Pain[a]	35.6[†]	6.9[†]	53.9[†]	9.0[†]
Erythema[a]	34.3[†]	8.6[†]	48.1[†]	4.3[†]
Swelling[a]	26.1[†]	4.5[†]	40.4[†]	2.8[†]
Pruritus	7.1	1.0	11.3	0.7
Warmth	1.7	0.3	3.7	0.2
Hematoma	1.6	1.4	1.6	1.6
Induration	N/A	N/A	1.1	0.0

In SPS, subjects ≥60 years of age received a single dose of either ZVL (n=19,270) or placebo (n=19,276); data presented is from

the Adverse Event Monitoring Substudy of SPS (n=3,345 received ZVL and n=3,271 received placebo). [3] In ZEST, subjects 50-59 years of age received a single dose of either ZVL (n=11,184) or placebo (n=11,212).[4] Subjects in the Adverse Event Monitoring Substudy of SPS and all subjects enrolled in ZEST were provided a vaccination report card to record AEs occurring through approximately 42 days postvaccination [3, 4, 11].

[a] Injection-site AEs solicited on the vaccination report card from Days 0-4 postvaccination.

Supplementary Annex 1:

Key Exclusion Criteria for SPS and ZEST

SPS Exclusion Criteria

A subject was not eligible to participate in this study if any of the following criteria apply:

1. Immunosuppression resulting from disease (e.g., malignancy; human immunodeficiency virus [HIV] infection), corticosteroids (except intermittent topical or inhaled corticosteroid [<800 mcg/day beclomethasone dipropionate or equivalent]), or other immunosuppressive/cytotoxic therapy (cancer chemotherapy or organ transplantation).
2. Active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that was stable in the absence of immunosuppressive/cytotoxic therapy).
3. Prior HZ.
4. Prior receipt of varicella vaccine.
5. Receipt of antiviral therapy at the time of enrollment, in order to avoid potential confounding of vaccine effectiveness.

ZEST – Exclusion Criteria

A subject was not eligible to participate in this study if any of the following criteria apply:

1. Prior receipt of any varicella or zoster vaccine.
2. Prior history of HZ.
3. An intercurrent illness that might interfere with the interpretation of the study.
4. Use of immunosuppressive therapy. Subjects on corticosteroids should be excluded if they were receiving or were expected to receive, in the period from 4 weeks prior to enrollment until 6 weeks postvaccination, systemic doses greater than required for physiological replacement, i.e., >5 mg of prednisone (or equivalent) for >2 weeks. Excluded immunosuppressive therapies also include chemotherapeutic agents used to treat cancer or other conditions, and treatments associated with organ or bone marrow transplantation. Subjects using topical or inhaled corticosteroids were eligible for enrollment.
5. Known or suspected immune dysfunction that is caused by a medical condition, or any other cause. Examples of medical conditions associated with immune dysfunction include congenital immunodeficiency, human immunodeficiency virus (HIV) infection, organ or bone marrow transplantation, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, or generalized malignancy. Subjects with a history of cancer who are not on active treatment and are not thought to be immunosuppressed at enrollment were eligible for enrollment. Note: Subjects with prostate or breast cancer who are not on chemotherapeutic drugs (other than hormone-blocking drugs), subjects with skin cancer who are not receiving radiation therapy or chemotherapy, and subjects with a history of

other malignancies who have been disease-free for at least 6 months, were eligible for enrollment.

MSD Clinical Trial Safety Data: Two Reports of VZV Oka/Merck Vaccine-strain, Confirmed by PCR

The first subjects, a 91 year old male, received ZVL at a potency of 34,000 PFU (ZVL licensed potency is >19,400PFU/dose) in a double-blind Phase I safety and immunogenicity study in which 176 subjects received one of six different potencies of vaccine or placebo; he reported a noninjection-site varicella-like rash at Day 17 postvaccination with a rash duration of 8 days, moderate in intensity with maximum of 21 lesions.

The second subject, a 23 year old varicella-naïve female, received a ZVL equivalent dose in a double-blind study that evaluated a high-titered dose of VARIVAX at a potency consistent with ZVL in subjects with no previous history of varicella; she reported a noninjection-site varicella-like rash with 5 lesions on Day 8 postvaccination.

Supplementary Annex 2:

Overview of Safety from Post-marketing Observational Studies

The real-world safety of ZOSTAVAX™ was evaluated in approximately 29,000 vaccinated individuals ≥60 years of age in a post-licensure cohort study.[21] The rate of all health outcomes occurring in the 42-day risk period (Days 1-42) following receipt of ZOSTAVAX™ was compared to that in a 90-day postvaccination self-comparison period (Days 91-180), using vaccinees as their own controls. Health outcomes were identified from diagnosis and procedure codes in the electronic medical records of hospitalizations and emergency room visits databases. Study data were reviewed by an independent Safety Review Committee composed of external experts who could request additional analyses or medical record reviews to further investigate potential safety signals. Medical record review and adjudication of all potential cases of stroke and myocardial infarction was conducted and identified no increased risk. No safety concerns were identified in this study of ZOSTAVAX™ in routine conditions of use.

The safety of ZOSTAVAX™ in routine conditions of use was also examined by the United States (U.S.) Centers for Disease Control and Prevention (CDC) in a large post-licensure observational study conducted in 8 managed care organizations participating in the Vaccine Safety Datalink network.[22, 23] Two self-comparison approaches, including a case-centered approach and a self-controlled case series analysis were used to assess the risk of pre-specified clinical events of interest. A total of 193,083 adults ≥50 years of age who received

ZOSTAVAX™ between 1 January 2007 and 31 December 2008 were included. Pre-specified events of interest were identified by diagnosis codes in health plan databases and included: stroke and cerebrovascular diseases; cardiovascular diseases; meningitis, encephalitis and encephalopathy; Ramsay-Hunt syndrome and Bell's palsy; and medically attended reactions (reactions leading to a medical visit). Different risk windows were used for different events. The risk of allergic reaction was significantly increased within 1-7 days of vaccination. No increased risk was found for the other events.

Supplementary Annex 3:

Post-marketing Surveillance for Reports from the Literature

MSD maintains a database of abstracts of published scientific literature related to MSD products and interests, including active substance(s) of MSD medicinal products. Articles to be abstracted are selected from alerting services such as Medline and EMBASE that are run weekly. The database is updated daily. Information from a literature source is entered into MARRS as an AE report if the following criteria are met: 1) an identifiable source that refers specifically to a published article in a scientific/medical journal, including relevant published abstracts from meetings, posters, and draft manuscripts which have been pre-approved for publication; 2) subject/patient or group of patients; 3) a suspected MSD product; and 4) an AE.

MedDRA Preferred Terms Selected in the Review of Post-marketing Reports of Common and Selected Adverse Experiences

Injection Site Reactions (ISRs): Injection site abscess, Injection site atrophy, Injection site bruising, Injection site cellulitis, Injection site cyst, Injection site dermatitis, Injection site discharge, Injection site discolouration, Injection site dryness, Injection site eczema, Injection site erosion, Injection site erythema, Injection site exfoliation, Injection site haematoma, Injection site hypersensitivity, Injection site hypoaesthesia, Injection site induration, Injection site inflammation, Injection site irritation, Injection site macule, Injection site mass, Injection site necrosis, Injection site nodule, Injection site oedema, Injection site pain, Injection site pallor, Injection site papule, Injection site paraesthesia, Injection site pruritus, Injection site reaction, Injection site streaking, Injection site swelling, Injection site ulcer, Injection site urticaria, Injection site warmth, Vaccination site abscess, Vaccination site bruising, Vaccination site cellulitis, Vaccination site discolouration, Vaccination site discomfort, Vaccination site erythema, Vaccination site haematoma, Vaccination site hypersensitivity, Vaccination site induration, Vaccination site inflammation, Vaccination site irritation, Vaccination site nodule, Vaccination site oedema, Vaccination site papule, Vaccination site paraesthesia, Vaccination site

pruritus, Vaccination site rash, Vaccination site reaction, Vaccination site swelling, Vaccination site urticaria, and Vaccination site warmth

Rash (overall): Rash, Rash vesicular, Rash pruritic, Rash papular, Rash pustular, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, and Rash papular

Hypersensitivity and Anaphylaxis: Standardized MedDRA Query (SMQ) for Anaphylactic Reaction (Preferred terms selected from the narrow SMQ: Anaphylactic reaction, Anaphylactic shock, Anaphylactic transfusion reaction, Anaphylactoid reaction, Anaphylactoid shock, Circulatory collapse, First use syndrome, Kounis syndrome, Shock, Type I hypersensitivity, Hypersensitivity, Angioedema, Allergy to vaccine, and Drug hypersensitivity)

Disseminated HZ: Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster meningoencephalitis, Herpes zoster necrotising retinopathy, and Varicella zoster pneumonia

Central Nervous System (CNS) events: Acute Disseminated Encephalomyelitis, Ataxia, Encephalitis, Encephalitis post varicella, Encephalitis viral, Encephalopathy, Meningitis, Meningitis aseptic, Meningitis viral, and Headache

Supplementary Table 3:

Supplementary Table 3: Post-marketing Reports (N=45) of Fatal Outcome Containing Sufficient Medical Information and/or Cause of Death from Market Introduction (02-May-2006) through 01-May-2016

(Of Note: 29 Reports Containing Insufficient Information to Determine Cause of Death are Not Included in the Table)

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
Deaths related to an underlying disease/condition						
88/M	Death, Exacerbated bronchitis	~16 days	Aortic stenosis, Chronic obstructive pulmonary disease (COPD), Dementia	Not listed. Reporter commented that the patient was taking a lot of medications.	Not specified.	Patient with COPD and dementia who 16 days postvaccination (pv) experienced an exacerbation of bronchitis and was admitted to the hospital. Per the report, vaccination with zoster vaccine, live (ZVL) had nothing to do with the exacerbation of the bronchitis or his hospitalization. Patient was released from the

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						hospital to hospice care and died at home.
93/F	Death, Medication error, Dyspnoea, Lung disorder	Unknown	Pneumonia, Urinary tract infection, Dementia, Hospitalization, Dehydration, Immunosuppression, Renal failure	Ceftriaxone	Urinary tract infection (UTI), Congestive heart failure (CHF)	Immunocompromised patient from a nursing home with recent hospitalization for pneumonia was hospitalized for a UTI. Following hospital discharge she was vaccinated with ZVL. Within the next 24 to 36 hours, the patient's lips turned blue and she died in the nursing home. The reporter was unsure of the official cause of death and could not recall how the death certificate was completed by the physician but she "thought that it was UTI and CHF".
74/F	Haemorrhage intracranial	4 days	Cardiac disorder, CVA	Unknown	Haemorrhage intracranial	Patient with medical history of heart problems, stroke and other unspecified medical conditions was vaccinated with a dose of ZVL. Several days later the pharmacy technician learned from the newspaper that the patient had passed away (4 days pv) with cause of death reported as non-traumatic intracranial hemorrhage. It was felt that the exposure to ZVL was a coincidental finding.
63/M	Coronary artery occlusion, Cardiac arrest. Coronary artery disease, Death, Fatigue, Hypertension, Myocardial fibrosis, Myocardial ischaemia, Sleep apnoea syndrome	3 days	Hypertension	Unknown	Coronary artery occlusion, Hypertension, Sleep apnoea, Cardiac arrest	Limited information was available. The patient died in his sleep 3 days pv, presumed cardiac arrest by autopsy. Autopsy report states cause of death as occlusive coronary artery disease with hypertension and sleep apnea as contributing factors.
65/F	Hypertensive heart disease, Coronary artery disease,	45 days	Asthma, Hypertensive heart disease, Coronary artery	Sitagliptin phosphate, Carvedilol, Naproxen,	Sudden death, Diabetes mellitus,	Patient found dead 45 days pv and 7 months after initiation of

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
	Diabetes mellitus		disease, Drug hypersensitivity,	Aspirin, Clonidine, Famotidine, Amlodipine Besylate, Valsartan, Nebivolol, Insulin aspart, Atorvastatin	Coronary artery disease, Hypertensive heart disease	sitagliptin phosphate (reported as suspect therapy). Approximately 10 days prior to death she was hospitalized for cardiac disease. The causes of death were reported as sudden death, coronary artery disease, hypertensive cardiovascular disease and diabetes.
81/M	Cardiac arrest, Asthenia, COPD, Coronary artery disease, Death, Dyspnoea, Respiratory tract congestion, Vomiting	2 day	Coronary artery disease, COPD Hypertension, Hyperlipidaemia, Cardiac failure congestive	Atorvastatin, Ramipril, Morniflumate, Carvedilol, Spironolactone	Cardiac arrest, COPD, Coronary artery disease	On the day of vaccination, the patient developed congestion/shortness of breath. The following day, the patient experienced vomiting and weakness and died. No autopsy was done. The cause of death was cardiac arrest, coronary artery disease, COPD.
75/M	Death, Unresponsive to stimuli, Aortic arteriosclerosis, Arteriosclerosis, Cardiac aneurysm, Coronary artery disease, Coronary artery occlusion, Cyanosis, Loss of consciousness	"Several hours"	Asthma, Myocardial infarction, Drug hypersensitivity, Hypercholesterolaemia	Influenza virus vaccine (unspecified), Hydrocodone	Atherosclerotic coronary vascular disease	The patient experienced sudden loss of consciousness several hours after vaccination. Autopsy report stated cause of death as atherosclerotic coronary vascular disease. The patient found unresponsive and cyanotic at bottom of ladder holding a drill (no malfunction). Arteriosclerotic cardiovascular disease findings: left axis deviation and circumflex arteries to pinpoint lumen; right coronary artery 80% narrowing; aorta with ulcerated plaque partly occluding left coronary ostium; previous myocardial infarction, extensive involving lateral left ventricle with aneurysmal thinning of ventricular wall.
70/F	Myocardial infarction	3 days	Breast cancer, Diabetes mellitus, Essential hypertension,	Bendrofluazide, Codeine phosphate, Paracetamol,	Myocardial infarction, Heart failure,	Patient died of suspected myocardial infarction. The death

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
			Uterine cancer	Letrozole, Lymecycline, Perindopril, Pravastatin, Nifedipine	Diabetes mellitus, Breast cancer, Hypertension	certificate, issued without an autopsy, reported the causes of death as myocardial infarction, heart failure, diabetes mellitus, breast cancer and hypertension.
69/M	Death, Lung neoplasm malignant, Hospice care, Herpes zoster	116 days	Herpes zoster, Drug hypersensitivity, Iodine allergy, varicella, Chronic obstructive pulmonary disease	acetaminophen (+) hydrocodone bitartrate, dicyclomine hydrochloride, methocarbamol, albuterol sulfate	Unknown	Patient with lung cancer in hospice case who developed HZ 104 days pv. The cause of death was unknown.
73/F	Systemic lupus erythematosus, Malaise, Feeding disorder, Lack of spontaneous speech, Medication error, Headache, Nausea, Cardiac arrest, Diarrhoea, Lung neoplasm, Dementia, Pain, Cerebral atrophy, Nervousness, Mental status changes, UTI, Dehydration	~7 months	UTI, Lung neoplasm malignant, Systemic lupus erythematosus, Hypertension	Sertraline	Cardiac arrest, Lung neoplasm malignant	Oncology patient who reported not eating as well, being shaky, "did not feel right", with daily headaches, and pain in the neck that radiated to her head. CT of the spine was performed and negative and a CT of the head showed mild cerebral atrophy and no metastasis. One month prior to her death she was hospitalized with altered mental status and possible cardiovascular accident. The discharge diagnosis included altered mental status, UTI, dehydration and a history of lung cancer. The causes of death were cardiac arrest and cancer with other significant conditions contributing to death.
82/M	Multi-organ failure, Cardiac arrest, Acute myocardial infarction, Coronary artery bypass, CVA, Seizure, Acute respiratory failure	~1 month	Smoker, Drug hypersensitivity, Abdominal pain, Adenocarcinoma of the prostate, Aortic valve replacement, Atherosclerosis of aorta, Basal cell carcinoma of skin, Hypertensive heart disease, Chronic kidney disease, Pacemaker, Bronchiectasis, Carotid	Acetaminophen ER, Aspirin, calcium plus D, fiber caps, Albuterol sulfate inhalation nebulizer, Ipratropium-albuterol inhalation solution, Levothyroxine, Metoprolol tartrate, Dronedarone, Simvastatin, Tiotropium bromide, Spironolactone, Vitamin D3 and Warfarin sodium.	Cardiac arrest, Multi-organ failure	Patient was hospitalized with non-ST elevation and myocardial infarct and developed acute respiratory failure. Patient found to have a mild positive troponin, underwent a coronary bypass. Following the procedure, he was ventilator dependent, pressor dependent and suffered a stroke with seizures. The patient experienced multi-

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
			atherosclerosis, Cerebral infarction/CVA, Cataract both eyes, Chronic constipation, COPD, Closed compression fracture of lumbar and thoracic vertebra, Grave's disease, Hearing loss, Hypercalciuria, Hyperlipidemia, Hypogonadism, Hypoxia, Iatrogenic hypothyroidism, Impaired fasting glucose, Right inguinal hernia repair, Intermittent claudication, diffuse Atherosclerotic cardiovascular disease, Peripheral vascular disease, Ischemic colitis, Ischemic enteritis, Joint pain, Mitral valve disorder, Neck strain, Peptic ulcer, Vagotomy, Secondary pulmonary hypertension, Tonsillectomy			organ failure and cardiac arrest. The patient died on in the hospital. The cause of death was reported as cardiac arrest and multi-organ failure, according to the death certificate.
68/F	Skin cancer	Unknown	Systemic lupus erythematosus, Merkel cell carcinoma	Unknown	Neoplasm malignant	Patient with lupus and Merkel cell carcinoma who 2 months pv experienced worsening and a progression of her cancer. The patient was hospitalized and died with cause of death reported as cancer.
75/F	Inflammatory carcinoma of the breast, Biopsy, Herpes zoster, Keloid scar, Metastasis, Rash pruritic, Rash vesicular, Scab	Unknown	Blood pressure abnormal, Blood cholesterol abnormal	Unknown	Metastatic inflammatory carcinoma of the breast	Patient experienced HZ (T8 dermatome) 7 days pv. Biopsy revealed inflammatory breast cancer. The HZ rash did not heal. Patient died from metastatic inflammatory breast cancer.
70/M	Death, HZ	~6 to12 months	Cardiac disorder, Hospitalization	Unknown	Cardiac disease	Patient with history of heart disease developed HZ ~ 6 days pv. Approximately 6 to 12 months pv the patient died presumably from heart disease but reporter did not know

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						for sure.
86/F	Sepsis, Palpable purpura, Vasculitis, UTI, Anaemia, Asthenia	2 months	Hypertension, Hyperlidaemia,, Diabetes mellitus, Spinal osteoarthritis, Eosinophil count increased, C-reactive protein increased	Pravastatin, Potassium chloride, Hydrochlorothiazide, Carisoprodol, Atenolol, Amitriptyline	Sepsis	Two weeks pv the patient experienced palpable purpura and vasculitis covering her body and was hospitalized 20 days pv for treatment. Following hospital discharge 2 days later, she developed a UTI and experienced profound weakness and anemia and was re-admitted. Following a prolonged hospitalization she developed sepsis and died 2 months pv of sepsis.
60/M	Septic shock, Cardiac arrest, Renal failure, Pancreatitis acute, Disseminated intravascular coagulation, Abdominal pain, COPD, Hyponatraemia, Anaemia, Diarrhoea, Cardiac disorder	5 days	Pancreatitis chronic, Smoker, Hypertension, Osteoporosis, Rhinitis allergic, Gastrooesophageal reflux disease, Asthma, Hypercholesterolaemia , Hyperglycaemia, Adverse drug reaction, COPD	Valsartan, hydrochlorothiazide, Pantoprazole, Venlafaxine, Amlodipine besylate (+) benazepril hydrochloride, Simvastatin, Prednisone, Budesonide, Albuterol sulfate (+) ipratropium bromide, Mometasone furoate, Albuterol, Estradiol, Ipratropium bromide, Vitamins, Calcium	Septic shock with the underlying cause of death as pancreatitis	Patient was hospitalized with diarrhea and abdominal pain, 3 days pv. Following insertion of a PICC line for intravenous fluids, she was reported to be obtunded, hypotensive, and was intubated because of an unstable airway. Shortly after arrival to the ICU she experienced a cardiopulmonary arrest. A CT scan of her abdomen was performed which showed mild necrotic pancreatitis on ultrasound. Her condition progressively declined. She was neurologically unresponsive and progressive declined and died 5 days pv.
75/F	Death, Mitral valve disease	48 hours	Cardiac valve disease, Hypertension, Mitral valve repair, Chronic atrial fibrillation, Hyperlipidaemia, Premature ventricular ectopic beats, Dilatation atrial, Right ventricular enlargement, Sinusitis	Pneumococcal Vaccine, Polyvalent (23-valent), Warfarin, Lisinopril, Digoxin	Mitral valve disease	Patient died 48 hours pv from mitral valve disease. No autopsy was done.
82/F	HZ, Encephalitis	40 days	Type 2 diabetes	Unknown	Encephalitis	Patient experienced HZ

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
	post varicella, Acute kidney injury, Acute respiratory failure, Cardiac failure congestive, Sinusitis, Pneumonia, Pleural effusion, Hiatus hernia, Malnutrition, Clostridium difficile infection, UTI, Meningitis viral		mellitus, Chronic renal insufficiency, Hypertension, Coronary artery disease, Asthma, Myocardial infarction, Hypothyroidism, Venous ulceration, Osteoporosis, Venous stasis, Angiomyolipoma, Arthritis, Anaemia of chronic disease, Drug hypersensitivity, Cataract operation, Shoulder operation, Lacunar infarction, Debility, Ischaemic cardiomyopathy		post varicella, HZ	and confusion 3 days pv. Her condition progressively declined and 30 days pv she was admitted to the intensive care unit. Upon discharge she was transferred to the long term unit where she passed away. The physician explained that the hospital records mention varicella encephalitis, and chickenpox complicated with encephalitis.
78/F	Acute myocardial infarction, Arteriosclerosis, Cardiac tamponade, Chills, Coronary artery thrombosis, Death, Feeling cold, Myocardial rupture, Nephrosclerosis, Pericardial haemorrhage, Pain	4 days	Hyperlipidaemia, Bronchiectasis, Chronic kidney disease, Osteopenia, Osteoporosis, Nephrotic syndrome, Acute renal insufficiency, Degenerative joint disease, Chronic diarrhea, Smoker, Respiratory insufficiency, Cardiac failure congestive	Diphtheria toxoid (+) tetanus toxoid	Hemopericardium with cardiac tamponade due to acute myocardial infarction rupture due to arteriosclerotic heart disease	Patient experienced aches, chills 3 days pv. Per family members the patient did not contact medical personnel nor feel need to seek emergency care. Patient was found dead by family 4 days pv. Autopsy report indicated that the cause of death was hemopericardium with cardiac tamponade due to acute myocardial infarction rupture due to arteriosclerotic heart disease.
92/M	Acute myeloid leukemia, Dyspnoea, Cardiomyopathy, Cardiac failure congestive, Pneumonia, Pleural effusion, Deep vein thrombosis, Constipation, Acute kidney injury, Epistaxis, Febrile neutropenia, Renal mass, Diarrhoea, Aortic aneurysm	~1 year	Coronary artery disease, Hypertension, Hypercholesterolaemia, Asthma, Osteoporosis, Drug hypersensitivity, Dyspnoea, Arthritis, Benign prostatic hyperplasia, Atrial fibrillation, Hiatus hernia, Coronary artery bypass graft, Cardiac pacemaker insertion, Cataract operation, Thyroidectomy, Prostatic operation, Deep venous thrombosis arm, Stent placement, Bradycardia, Ex-	Albuterol, Aspirin, Morniflumate, Furosemide, Lisinopril, Potassium chloride, Nitroglycerin, Panolazine hydrochloride, Montelukast sodium, Atenolol, Fluticasone propionate (+) salmeterol xinafoate, Isosorbide mononitrate, Folic acid, Finasteride, Allopurinol	Cardiomyopathy	Patient presented to the office 10 months pv with shortness of breath and was diagnosed with acute myeloid leukemia. Diagnoses on admission to the hospital included: acute myeloid leukemia, pneumonia, pleural effusion, asthma, left upper extremity deep venous thrombosis, constipation, urinary retention, acute renal failure, hypertension, epistaxis and neutropenic fever central. The patient was discharged from the hospital only to be re-

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
			smoker			admitted ~ 1 month later (~. 1 year pv) with shortness of breath for 3 days. CT of the chest showed no pulmonary emboli, but bilateral pleural effusions consistent with pulmonary edema. A chest x-ray showed infiltrate in the right lung consistent with pneumonia. 2-D echo showed an ejection fraction of 15% with mild aortic stenosis. Cardiology assessment was acute decompensated heart failure. Following hospital discharge patient was admitted to hospice and died within 1 month of hospice from cardiomyopathy.
Deaths related to cardiac disorder						
Unknown /F	Cardiac infection, Rash	Unknown	Immunodeficiency, Discomfort	Unknown	Cardiac infection	Patient developed a cardiac infection shortly pv and died from the infection. It was reported that the patient may had been immunodeficient prior to receiving ZVL. She may also have developed a rash. Neither the presence of immunodeficiency nor the development of a rash had been confirmed.
64/F	Myocardial infarction	1 day	Unknown	Unknown	Cardiac arrest	Patient died of heart attack on day of vaccination. There was no background of any cardiovascular disease. Cause of death was cardiac arrest.
Unknown / Unknown	Myocardial infarction	~1 week	Unknown	Unknown	Myocardial infarction	Patient died 1 week pv of a heart attack. No other information was provided.
Unknown /F	Myocardial infarction	Unknown	Unknown Reporter comment: “some health troubles”	Unknown	Myocardial infarction	Patient with a history of cardiac disease who died on an unknown date pv. No other information was provided.

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
71/F	Myocardial infarction, Cough	3 months	Renal transplant, Hypertension, Osteopenia	Ramipril, Anitidine, Amlodipine, Aspirin, Atorvastatin, Prednisolone	Myocardial infarction of left ventricle	Patient sought medical care 21 days pv for a dry cough that had been present for ~ 3-4 weeks (exact onset unknown). She was hospitalized 3 months pv and died from a myocardial infarction of the left ventricle.
80/M	Acute myocardial infarction, Arteriosclerosis coronary artery, Seizure, Confusional state, Chest discomfort, Agitation, Malaise, Decreased appetite, Diarrhoea, Vomiting, Pain, Incorrect route of drug administration, Vaccination error	5 days	Asthma, Hypertension, pernicious aenemia, Dextrocardia, Family history of ischaemic heart disease for people 60 years aged and over	Budesonide formoterol, Hydroxycobalamin, Terbutaline, Salbutamol inhaler, Bendofluazide	Arteriosclerosis coronary artery, Myocardial infarction	It was reported that the patient had a “fit” (seizure) lasting for 5-10 min on an unreported date pv. The patient was very confused and agitated afterwards. Since then, he had been a generally unwell; not eating and drinking properly, and intermittently having central chest tightness, which went across his shoulder and to his neck. He then proceeded to developed diarrhea and vomiting. Five days pv, the patient had an acute myocardial infarction and was taken to the emergency room (ER). Prior to arrival at the ER, the patient had pulseless electrical activity (PEA) for approximately 4 min and cardiopulmonary resuscitation (CPR) initiated and patient was intubated. Saturations started to improve but the circulation was in arrest. Glasgow Coma Scale was 3/15 and pupil was fixed with BM: 6.4. The patient had no rash or track marks for cellulitis. All the reversible causes were corrected as possible with calcium chloride 10 mL intravenously as the patient had potassium chloride 6.7.

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						The patient's rhythm remained in PEA. ECG showed ST elevation on right side of inerfero-laleral, aorta scan was done and the abdominal aortic aneurysm (AAA) size was measured: 2.7cm approximately. The patient had output after 12 minutes of CPR. Then, post-resuscitation care was started. Intravenous therapy started and blood gases were done. However, the patient had another cardiac arrest and was not responding to ionotropic support. CPR was started again but after 2 cycles it was decided with the health team to stop the CPR as there was no change in the rhythm and no sign of life. The patient was pronounced dead (5 days pv).
62/F	Death, Chest discomfort, Dyspnoea, Eosinophilic myocarditis, Hyperhidrosis, Hypersensitivity, Myocarditis	28 days	Deep vein thrombosis, Diabetes mellitus, Hypertension, Environmental allergies	Simvastatin, Metformin, Losartan potassium, Aspartic acid	Eosinophilic myocarditis	Patient presented to the ER 17 days pv with diaphoresis, chest tightness and shortness of breath. The patient died 11 days later. Autopsy confirmed eosinophilic myocarditis with unknown etiology.
70/F	Sudden death, Cardiovascular disorder, Death, Vomiting, Circulatory collapse	6 days	Unknown	Ranibizumab, MacuLEH plus, MacuLEH, MacuShield	Circulatory collapse	Patient experienced vomiting 4 days pv. She seemed to be improving but 6 days pv she developed circulatory collapse and died. The post mortem done was an external examination only, along with the police report and perusal of the medical records. It was the opinion of the pathologist that the patient had died of natural causes, namely cardiovascular degeneration. An

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						autopsy was performed.
77/M	Myocardial infarction, Pemphigoid, Abasia, Fall, Incorrect route of drug administration	9 months	Neuromyopathy	Unknown	Myocardial infarction	Patient had neuro-muscular degenerative disorder and reported to have a weakened immune prior to vaccination. He developed bullous pemphigoid 6 months after vaccination. Nine months pv the patient died from a myocardial infarction.
91/F	Cardiac arrest, Malaise, Diarrhoea, Pain in extremity	5 days	Inflamed seborrhoeic keratosis, Polymyalgia Rheumatic, Bell's palsy, Cerumen impaction, Ear pain, Headache, Hyperlipidaemia, Hypothyroidism, Urinary frequency, Constipation, Dysphagia, Chest pain, Urinary incontinence, Allergy to ciprofloxacin hydrochloride and penicillin, history of acute myocardial infarction	Levothyroxine sodium, Simvastatin, Vitamins, Glucosamine sulfate, Aspirin, Calcium (+) vitamin D, Vitamin E, Ascorbic acid, Omega-3 marine triglycerides, Prednisone	Cardiac arrest	Two to three 3 days pv the patient complained of arm pain and diarrhea. The patient was found dead at home five days pv. The cause of death was cardiac arrest. No autopsy was performed.
85/M	Respiratory failure, Herpes zoster (HZ), Cerebrovascular accident (CVA), Cardiac arrest, Anemia, Dysphagia, Fall, Asthenia, Tympanic membrane perforation	13 days	Atrial flutter, Arthritis, Mental impairment, Hyperlipidaemia, Back pain, Large intestine polyp, Compression fracture, Dementia, Gastrooesophageal reflux disease, Amnesia, Osteoporosis, Dyspnoea, Cardiac failure congestive, Constipation, Inguinal hernia, Visual disturbance, Diverticulosis, Ejection fraction decreased, Thyroid disorder, Rhinitis allergic, Abdominal pain, Arthralgia, Sinus congestion, Cardiovascular disorder, Herpes zoster, Aortic regurgitation, Nocturia, Fall,	Alendronate sodium, Amiodarone, Furosemide, Carvedilol, calcium Carbonaet, Senna, Levothyroxine, Aspirin, Omeprazole, Donepezil Hydrochloride, Naproxen	CVA, Cardiac arrest, Respiratory failure	Patient with extensive medical history and multiple concomitant therapies. Two to three days pv the patient was diagnosed with acute vesicular rash, suspected shingles and ear drum perforation. Acetaminophen (+) propoxyphene napsylate, famciclovir, and "Medrol Dosepak" were prescribed. Eight days pv the patient presented to the emergency room after multiple falls and complaining of weakness and inability to ambulate or bear weight, severe pleuritic type chest pain, which was described as sharp, and tenderness anteriorly in the right chest. The intensity was

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
			Squamous cell carcinoma, Gastrointestinal haemorrhage, Colitis, Cholecystectomy			assessed as mild, and the symptoms were reproducible upon palpation of the patient's chest. The patient was admitted to the hospital for sudden onset of weakness, multiple falls and anemia. The following day he intubated after suffering a cardiopulmonary arrest. Chest X-ray that showed a new right perihilar and increasing left lower lobe opacities, thought to be either secondary to pneumonia or pulmonary edema. Patient was successfully extubated but continued to decline and per the family's request orders were established to be a do not resuscitate (DNR). Chest X-ray done 13 days pv showed increasing consolidative changes in the left mid and lower lung fields. The patient died day 13 pv following sudden onset of bradycardia followed by asystole. The physician reported because of the patient's age, DNR status, and other underlying conditions, he did not believe the zoster vaccine live (Oka/Merck) caused the CVA or the patient's death. The cause(s) of death as reported on the certificate of death were as follows: respiratory failure, cardiac arrest and CVA.
Death related to infection						
Unknown / Unknown	Epstein-Barr virus infection	Unknown	Lymphoma, Status post bone marrow transplant	Unknown	Epstein Barr virus infection	On an unknown date, after receiving ZVL, the patient died of possible complications

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						of Epstein Barr virus syndrome. No autopsy performed. No other information provided.
60/M	HZ disseminated, Disease complication, Drug prescribing error, Medication error	Unknown	Cancer	Unknown	HZ disseminated, Disease complication	Patient died due to complications due to disseminated zoster virus. Patient was reported to be "likely immunocompromised."
65/M	VZV infection, Abdominal pain, Respiratory distress, Sepsis, Shock, Pulmonary mass, Oesophageal candidiasis, Varicella virus test negative, Drug administration error	48 days	Non-Hodgkin's lymphoma, Chronic respiratory disease, Hypertension, Anaemia, Tobacco user	Pneumococcal 13v conj vaccine (CRM197), Bendamustine, Methylprednisolone, Trimethoprim sulfate, Ceftriaxone sodium	Shock	Patient with non-Hodgkin lymphoma (under bendamustine chemotherapy in the last five months) previously hospitalized because of a possible pulmonary nocardiosis and treated with ceftriaxone and trimethoprim sulfa. Patient was hospitalized 5 days pv due to abdominal pain and speculated worsening lung nodules with airway compromise (possible esophageal candidiasis). The patient developed a rash 37 post-vaccination. The same day the patient was diagnosed with sepsis. PCR of alveolar liquid was positive for VZV in lung. A skin biopsy was performed showing VZV. Testing to determine if the virus strain of VZV was wild-type or vaccine-strain was not performed. PCR of CSF provided no results. Patient died 48 days pv, "with a refractory shock." Autopsy results were not reported.
83/F	Pneumonia, HZ	2 month	Unknown	Acyclovir, Clorazepate dipotassium	Pneumonia	Seven days pv the patient developed HZ. The patient was treated and made a full recovery. Subsequently she developed pneumonia and died 2 months pv.

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
79/M	HZ disseminated, Varicella zoster virus (VZV) infection, Pneumonitis, HZ meningoencephalitis, Acute hepatic failure, Respiratory failure, Multi-organ failure, Medication error. Confusional state, Lethargy, Malaise, Skin lesion, Thrombocytopenia, Neutropenia, Histiocytosis-haematophagic, Jaundice, Skin haemorrhage, Fall, Contraindication to vaccination, Pyrexia, Rash vesicular, Influenza-like illness	~2 months	Chronic lymphocytic lymphoma (CLL), Pneumocystis pneumonia, Hypertension, Fever of unknown origin, Pyrexia, Fatigue, Neutropenia, Drug reaction	Lisinopril, Timolol maleate, Aspirin	Multi-organ failure, HZ disseminated	Patient with CLL treated with cyclophosphamide, fludarabine and rituximab ~ 5 months pre-vaccination. [30] Approximately 2 weeks pv patient felt unwell and received antibiotics for flu-like symptoms, and lethargy. Approximately 37 days pv, he developed a pustular rash and was hospitalized and treated with IV acyclovir for VZV infections. Approximately 42 days pv the patient was intubated for respiratory failure. Subsequently, he developed fulminant liver failure which progressed to multi-organ failure. PCR analysis of a skin specimen was positive for VZV Oka/Merck vaccine-strain. VZV was detected from plasma and BAL with no strain identification reported.
Death related to Central Nervous System (CNS) event						
72/M	Acute disseminated encephalomyelitis (ADEM), Mental impairment, HZ, Hypophagia	1 month	Dementia, Parkinson's disease, Dry skin,	Bisacodyl, Chlorhexidine gluconate, Daktarin, Fludrocortisone, Lactulose, Lansoprazole, Nutritional supplement, Paracetamol, Rivastigmine, Sertraline, Simvastatin, Sinemet, Zerobase	Acute disseminated encephalomyelitis	Two days pv the patient experienced sudden and severe deterioration in mental functions. 16 days pv HZ was diagnosed. Patient was admitted by the HCP with suspected ADEM. No specimens were sent for PCR or culture and no results from laboratory or imaging studies were reported. Initially treated with acyclovir. The patient stopped eating and was discharged to home on hospice with the diagnosis of terminal Parkinson's disease. Patient died one month

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						pv. Reported cause of death was acute disseminated encephalomyelitis. No autopsy reported.
86/M	Aneurysm ruptured, Cardiac arrest, Cerebral haemorrhage, Death, Endotracheal intubation, Foreign travel, Lethargy, Unresponsive to stimuli	5 days	None	Pneumococcal vaccine, Polyvalent (23-valent), Influenza virus split virion 3v vaccine inactivated	Subarachnoid haemorrhage, Aneurysm ruptured	Five days pv the patient presented to the hospital with lethargy. Upon arrival, the patient was oriented and then had an acute decompensation. He did not response to voice or sternal rub and had no cough or gag reflex. He experienced bradycardia, asystole and was intubated. A CT scan showed diffuse subarachnoid hemorrhage resulting from an anterior inferior cerebellar artery aneurysm rupture that occurred two days prior to hospital admission, "or before". The family declined further care. Cause of death was subarachnoid hemorrhage from a ruptured aneurysm.
74/F	CVA	Unknown	Cardiac disorder, Asthenia, Overweight, Blood cholesterol abnormal	Unknown	CVA	Patient died due to a stroke that was considered by the reporter as not related to vaccination with ZVL.
79/M	CVA	7 day	Type 2 diabetes mellitus, Hypertension, Parksinsonism, Atrial fibrillation	Unknown	CVA	Patient died due to stroke that was considered as not related to zoster vaccine live (Oka/Merck) injection.
Other causes of death						
~69/F	Pulmonary embolism, Pulmonary fibrosis	6 weeks	Pulmonary fibrosis	Prednisone	Pulmonary embolism, Pulmonary fibrosis	The patient died six weeks pv. The pharmacist did not say if there were any complications or adverse events between the time she was given the vaccination and the time of her death or if the patient had been hospitalized for any

Age (Yrs)/Sex	Reported AEs	Time between Vaccination and Death	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Cause of Death	Additional Case Information
						reason. The patient was taking prednisone at the time of her death. Pulmonary fibrosis was also reported as cause of death.
75/F	Thrombosis	~1-2 year	Unknown	Unknown	Thrombosis	The patient was vaccinated with ZVL in 2009 and in 2010. The patient died on 19-SEP-2011 from a blood clot. The reporter stated that she didn't feel the death had anything to do with the vaccinations.
86/F	Road traffic accident, HZ, Injection site infection	16 days	Unknown	Unknown	Road traffic accident	Patient experienced HZ, 4 days pv. On an unknown date in the same month, the patient experienced an injection site infection. The patient was treated with anti-virus medicine, steroids, pain medicine, and gabapentin. Patient died in a car accident, 16 days pv. It was unknown if autopsy was done.
80/M	Multi-organ failure, Death, Pyrexia	21 day	Temporal arteritis, Left cataract (extraction), Artery biopsy, Chest pain, Musculoskeletal chest pain, Lower respiratory tract infection	Betamethasone valerate, Amoxicillin, Cholecalciferol, Lansoprazole, Polyethylene glycol, Prednisolone	Multi-organ failure, Death unexplained. Fever	The patient developed a fever on the day of vaccination. The patient was admitted to the hospital seven days pv and subsequently died of multi-organ failure 21 days pv. The reported causes of death were death unexplained, fever and multi-organ failure.
Unknown/ Unknown	Death, Surgery, Pyrexia	Unknown	Unknown	Diphtheria toxoid (+) pertussis whole cell vaccine (+) tetanus toxoid, Influenza virus split virion 3v vaccine inactivated	Unknown	On an unknown date pv the patient developed a fever and died following surgery. No other information was provided.
Abbreviation key: AE=adverse experience; F=female; M=male; PCR= polymerase chain reaction						

Supplementary Table 4:

Supplementary Table 4: Summary of 10 Reports of Ophthalmic Herpes Zoster (HZO) in Patients with a Prior History of HZO

Age (years)/ Gender	Time Interval between prior HZO and ZV	Time-to-onset of HZO pv	Significant Medical History	Event Seriousness /Outcome[a]
82/F	12 years & 5 years	4 days	2 prior episodes of HZO; large corneal ulcer with episode pv	Serious/NR
63/F	4 years	1 week	Immune system disorder; on daily valtrex for 4 years; dose withheld for 2 weeks pv; episode pv reported as diffuse interstiitial keratitis	Serious/NR
59/M	~ 1 year	13 days	History of HZ	Non-serious/ Not recovered
63/F	~ 1 year ago and recurrent	4 days	None	Non-serious/ Recovered
90/F	NR	1 year	None	Non-serious/ Recovered
50/F	8 episodes within 5 years	35 days	Literature report; on daily acyclovir and recurrent tapers of loteprednol with flares of HZO; episode of HZO pv described as severe worsening of stromal keratitis [33]	Non-serious/ Recovered
NR/NR	NR	NR	Literature report; immune deficiency [33]	NR/NR
NR/NR	NR	NR	Literature report [33]	NR/NR
NR/NR	NR	NR	Literature report[33]	NR/NR
NR/NR	NR	NR	Literature report [33]	NR/NR

Abbreviations: VZV=varicella-zoster virus; HZO=ophthalmic herpes zoster; pv=postvaccination; M=male; F=female; NR=not reported; ~approximately
[a] outcome at the time of the report;

Supplementary Table 5a and 5b

Supplementary Table 5a: Summary of Post-marketing Reports of Encephalitis Received From Market Introduction (2-May-2006) Through 1-May-2016

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
Encephalitis (n=14)							
64/M	Encephalitis, Dysphagia, Dysphonia, Respiratory failure	~3 months	Hypertension, Penicillin allergy	Unknown	No	Recovering	Patient vaccinated with influenza vaccine 1 month prior and pneumococcal 23v polysaccharide vaccine same month as ZVL. Three months postvaccination (pv) patient experienced dysphagia, hoarseness and dyspnea. Symptoms worsened and 4 months pv patient was diagnosed with encephalopathy, hospitalized for respiratory failure and intubated. Serum IgG and IgM antibodies reported to be positive for VZV with CSF reported to be negative for VZV by PCR. Patient recovered and was discharged 5 months pv. Approximately 8 months pv symptoms recurred and patient was hospitalized again. Per the reporter, the patient has been in and out of the hospital with trouble swallowing and a "variety of other issues". At time of the report, patient was recovering.
79/F	Meningitis, HZ, Pneumonia,	6 hours	Drug hypersensitivity, Meningitis	Furosemide, Diclofenac	No (CSF: wild-type VZV)	Recovered	Patient experienced dull pain behind right

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
	Encephalitis, Varicella						eye and right side of throat 6 hours pv; 72 hours pv vescicular lesions observed on throat along with T 39.5, hoarseness, coughing, and fatigue reported. Pneumonia and varicella meningoencephalit is was diagnosed 96 hours pv. Lumbar puncture revealed an elevated white cell count and negative PCR for VZV. A repeat PCR of CSR was reported as positive for wild type VZV.
61/ Unknown	Encephalitis, Mental status changes	7 days	Unknown	Unknown	No	Unknown	Patient was diagnosed with altered mental status and encephalitis 7 days pv and hospitalized. Lumbar puncture showed zero white blood cells, 1 red blood cell, protein 47 (unit not provided) and glucose 83 (unit not provided). Lumbar puncture was repeated showing an elevated protein at 70, otherwise no change. Therapy with anti-seizure medication and "high" steroids was begun.
67/F	Encephalitis, Diverticulitis	6 days	Chronic back pain, Hypothyroidism , Incontinence,	Aspirin, Levothyroxine, Vitamin D, Vitamins, Amoxicillin (+)	No (CSF-inadequate specimen, no strain identified.	Recovered	Patient experienced myalgia, fatigue, general weakness and speech aphasia

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
			Diverticulitis, Drug hypersensitivity, Hypertension	clavulanic acid	DNA was also extracted and the result was still negative)		6 days pv and was seen in the ER. Amoxicillin (+) clavulanic acid that was started prior to ER visit was discontinued. CSF showed: 15 white blood cells (WBC) (mostly monocytes and some neutrophils), protein 128, glucose 65 and negative culture. Therapy with acyclovir and dexamethasone was intitated. MRI was reported as negative. Lumbar puncture was repeated and showed CSF with 50 WBCs. CSF for PCR analysis was reported as inadequate to detect VZV and extracted DNA was reported as negative. Encephalitis was diagnosed. Triple antibiotic regimen for bacterial meningitis was begun
59/F	Encephalitis viral, Inappropriate schedule of drug administration	3 days	Varicella, Neuralgia, Haemorrhage intracranial	Gabapentin, Naproxen, Black cohosh, Allergenic extract	No (CSF: wild-type VZV)	Recovered	Patient developed fever, joint aches, and mental status changes 3 days pv and was hospitalized with diagnosis of viral encephalitis. PCR of CSF was confirmed to be wild-type VZV.

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
69/F	Encephalitis, Ophthalmic HZ, HZ, Vasculitis	24 days	Menopause, Hypertension, Gastrooesophageal reflux disease, Type 2 diabetes mellitus, Plantar fasciitis, Hyperlipidaemia, Monoplegia, Seasonal allergy, Depression, Anxiety, Drug hypersensitivity	Glyburide, Metformin, Gemfibrozil, Pravastatin, Bisoprolol Hydrchlorothiazide, Olmesartan medoxomil, Escitalopram oxalate, Aspirin, Fexofenadine	No	Recovering	Patient developed HZ 4 days pv that progressed to involve her eye (no rash, but pus & drainage from eye and blisters above eye). Patient was hospitalized 24 days pv, and underwent a lumbar puncture with results reported as: "pleocytosis of the CSF along with episodic confusion suggests vasculitis or encephalitis."
61/M	Encephalitis, Delirium, Mental status changes, Abscess	2 days	Latex allergy, Drug hypersensitivity	Unknown	No	Recovered	Patient experienced mental status changes and delirium 2 days pv and was hospitalized for 7 days. Discharge diagnosis, initially reported as encephalitis, was determined to be delirium. Per the reporter symptoms were induced by an abscess in sinuses.
75/M	Encephalitis, HZ	23 days	Hypertension, Alcohol use, Bipolar disorder	Lisinopril, lithium, paroxetine and naltrexone hydrochloride	No	Recovering	Patient developed HZ within 1 week pv. Patient was hospitalized with "altered mental status" 30 days pv. Meningoencephalitis was diagnosed and acyclovir started. Per the report: "a lumbar puncture and several other laboratory tests" were done but results were not provided.
Unknown	Encephalitis	11 days	Unknown	Unknown	Unknown	Unknown	Limited

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
/M							information was reported. Patient was reported to have been admitted to the intensive care unit for encephalitis day 11 pv.
72/F	Encephalopathy, Abdominal pain, Aphasia, Chills, Confusional state, Dysphagia, Encephalitis, Hallucination, HZ, Mental status changes, Neurogenic bladder, Pruritus, Pyrexia, Sepsis, Urinary tract infection (UTI)	Unknown	Type 2 diabetes mellitus, Hypertension, Gastroesophageal reflux disease, Recurrent UTI	Venlafaxine, Candesartan cilexetil tablet, Pioglitazone, Lansoprazole, Celecoxib, Insulin glargine, Metformin, Aspirin	No (CSF negative for VZV)	Recovered	Patient experienced dysphagia, confusion, mental status changes, hallucinations and lesions consistent with HZ on an unknown date pv. Blood culture was positive for polymicrobial sepsis with *Pseudomonas* species, *E.coli*, and *Proteus.* On an unspecified date encephalitis, possibly related to VZV was diagnosed. Acyclovir was started and encephalopathy resolved. CSF was negative for VZV.
73/F	HZ, Encephalitis	5 years	Unknown	Unknown	Unknown	Unknown	Limited information was reported; patient was hospitalized for HZ and encephalitis 5 years pv
Late 60's/F	Death, Renal transplant, Encephalitis, Varicella	~4 months	Unknown	Unknown	Unknown	Died	Limited information was reported. Patient underwent a renal transplant 2 months pv. Varicella and encephalitis were diagnosed 4 months pv. Cause of death were not reported but patient died

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and Encephalitis Symptoms	Medical history/ Concurrent conditions	Concomitant therapy(ies)	Oka/Merck Vaccine-strain VZV Confirmed by PCR on CSF (Yes/No)	Outcome	Additional Case Information
							approximately 3 years pv.
69/F	Encephalitis, Surgery, Hypoaesthesia, Pain, Amnesia, Confusional state, Paraplegia, Intervertebral disc protrusion, Transaminases increased	Unknown	HZ, Thoracic operation	Oxycodone, Morphine	Unknown	Unknown	Patient experienced numbness throughout body and left sided pain, encephalitis, terrible memory loss, and confusion on an unspecified date pv. A slipped disc was also reported,
Unknown/ Unknown	Encephalitis	Unknown	Unknown	Unknown	Unknown	Unknown	Limited information reported; encephalitis was reported without details

Supplementary Table 5b: Summary of Post-marketing Reports of Acute Disseminated Encephalomyelitis (ADEM) Received From Market Introduction (2-May-2006) Through 1-May-2016

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and ADEM	Medical history/ Concurrent conditions	Concomitant therapy(ies)	ADEM Confirmed by Labs or Image Studies (Yes/No)	Outcome	Additional Case Information
Acute Disseminated Encephalomyelitis (N=3)							
72/M	Acute disseminated encephalomyelitis (ADEM), Mental impairment, HZ, Hypophagia	2 days	Dementia, Parkinson's disease, Dry skin,	Bisacodyl, Chlorhexidine gluconate, Daktarin, Fludrocortisone, Lactulose, Lansoprazole, Nutritional supplement, Paracetamol, Rivastigmine, Sertraline, Simvastatin, Sinemet, Zerobase	No No laboratory or imaging reported	Died	Patient experienced sudden and severe deterioration in mental functions, 2 days postvaccination (pv). HZ was diagnosed16 days pv. Patient was admitted with suspected ADEM. No specimens were sent for PCR or culture and no results from laboratory or imaging studies were reported. Initially treated

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and ADEM	Medical history/ Concurrent conditions	Concomitant therapy(ies)	ADEM Confirmed by Labs or Image Studies (Yes/No)	Outcome	Additional Case Information
							with acyclovir. The patient stopped eating and was discharged to home on hospice with the diagnosis of terminal Parkinson's disease. Patient died one month pv. Reported cause of death was ADEM. No autopsy was reported.
62/M	ADEM, Cerebrovascular accident (CVA), Cerebral small vessel ischemic disease, Guillain-Barre syndrome, Loss of gag reflex, Acute respiratory failure, Plasmapheresis, Pneumonia, Tracheostomy tube insertion, Pulmonary oedema, Hypocalcemia, Gastritis, Hypertension, Urinary tract infection pseudomonal, Fall, Scalp laceration	7 days	Hypertension, Joint instability, Hyperlipidemia, Dysplipidemia	Aspirin, Atorvastatin calcium, Fosinopril sodium	No No laboratory test confirming VZV or suggestive of ADEM were reported. MRI done at 4 month pv, was compared to MRI done 10 days pv, showed: decrease in signal intensity along the anterior caudal aspect of the pons suggested a small area of encephalomal acia change at this level without suspicious enhancement or suspicious altered signal intensity on diffusion imaging; mild amount of increased T2-Flair weighted signal remaining within the	Recovered	Patient was seen in ER twice for trouble speaking and left sided weakness day 7 pv. Blood pressure was elevated at 162/95. CT of the head showed mild degree of diffuse cerebral atrophy but no hemorrhage or ischemic infarct. CVA was diagnosed and patient was hospitalized. MRI showed cortical atrophy of the brain with findings suggestive of small vessel ischemic changes and a possible old lacunar infarct. Electroencephalogr am (EEG) showed 5-6 hertz theta slowing and sharp transients. Patient's right sided hemiparesis and severe dysarthria occurred on day 8 pv. No changes in MRI. On day 9 pv symptoms progressed to include left sided weakness, sensory

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and ADEM	Medical history/ Concurrent conditions	Concomitant therapy(ies)	ADEM Confirmed by Labs or Image Studies (Yes/No)	Outcome	Additional Case Information
					white matter bilaterally and may represent a mild amount of white matter ischemic change bilaterally (differential diagnosis would be minimal inflammatory or demyelinative changes). No significant signal abnormality and no suspicious areas of enhancement on postinfusion imaging; mild cerebral atrophy and mild mucosal thickening in a few scattered paranasal sinuses.		deficit, loss of gag reflex and trouble breathing requiring intubation. Guillain-Barre syndrome with respiratory failure was diagnosed. Electromyography and nerve conduction were normal. There was no electro-diagnostic evidence of acute demyelinating polyneuropathy. Lumbar puncture was consistent with Guillain-Barre syndrome. Plasmapheresis was started. Gag reflex improved and patient was extubated but continued to be tachypnic with respiratory distress. Tracheostomy placed. Pulmonary edema and pneumonia were diagnosed. Patient continued to improve and was transferred to a rehabilitation unit. ADEM was listed as a diagnosis in rehabilitation unit notes under speech and physical therapy. Patient continued to improve and was discharged from rehab.
Unknown	ADEM	Unknown	Unknown	Unknown	Unknown	Unknown	Report received from a pharmacist that a patient developed ADEM. No details were reported or

Age (Yrs)/ Sex	Reported AEs	Time between Vaccination and ADEM	Medical history/ Concurrent conditions	Concomitant therapy(ies)	ADEM Confirmed by Labs or Image Studies (Yes/No)	Outcome	Additional Case Information
							available.

Supplementary Figure 1:

Supplementary Figure 1: Post-marketing Reports of Fatal Outcome Temporally-associated with Vaccination with ZVL and Reported by Cause of Death